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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/541,263	HOUSEY, GERARD
	Examiner	Art Unit
	CHRISTINA BORGEEST	1649

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16 and 18-27* is/are pending in the application.

4a) Of the above claim(s) *25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-24 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 December 2010 has been entered.

Claims 16, 18-23 have been amended; claim 17 has been cancelled; claims 25 and 26 remain withdrawn and claim 27 is new. Claims 16, 18-24 and 27 are under examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) and 365(c) is acknowledged. Based on the information given by Applicant and an inspection of the prior applications, the Examiner has concluded that the subject matter defined in the instant claims is supported by the disclosure in provisional application serial no. 60/437,377, filed on 2 January 2003 because the claimed invention is disclosed in said application. Further, the Examiner has concluded that the subject matter defined in the instant claims is supported by the disclosure in PCT/US2003/041745, filed on 31 December 2003. Thus, priority date of claims 16, 18-24 and 27 of the instant application is deemed to be 2 January 2003.

Rejections Withdrawn

Note: All previous rejections over claim 17 are hereby withdrawn in response to Applicant's cancellation of that claim.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 16 and 18-24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention as set forth in the previous Office action mailed 7 June 2010 is withdrawn in response to Applicant's amendment of the claims. Specifically:

Claim 16 no longer recites "wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2."

Claim 18 no longer recites the limitation "protein of interest", thus has sufficient antecedent basis.

Claims 19-23 no longer recite the limitation "host cell", thus have sufficient antecedent basis.

Claim 21 no longer recites the phrase "the host cell essentially does not produce the protein."

New Rejection/Rejections Maintained

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. ***This rejection was necessitated by amendment.*** Specifically, claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There is no step describing how the characteristic of the small molecule, namely that it "cannot bind to the non-IRS2 proteins in the absence of IRS2" was determined ***before*** carrying out the entire method. The preamble recites the goal of "determining whether a small molecule is an activator or an inhibitor of IRS2," and the instant specification at paragraph [0032] defines:

> By activator or inhibitor of IRS2 is meant a small molecule that binds to IRS2 alone and activates or inhibits the signaling function of IRS2, or a small molecule that binds to a complex comprising IRS2 and other cellular proteins and wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2.

Thus, the goal of the claim is to determine whether the small molecule is an activator or an inhibitor of IRS2 and the specification defines activators or inhibitors of IRS as small molecules that bind to IRS2 alone or a small molecule that binds to a complex comprising IRS2 and other cellular proteins and wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2. It is clear from the discussion in the specification that the limitation is meant to define the activator of IRS2 that is identified by the claimed method. As such, there is gap in the steps between the goal or

preamble of the claim, namely, determining whether the small molecule is an activator or an inhibitor and the portion of the claim that already recites the required characteristic of activators or inhibitors. It is not clear how is this characteristic determined before carrying out the method. The claim encompasses a thought process whereby it is known in advance of carrying out the screening assay that the small molecule has the very characteristics sought by carrying out said screening assay. For the purposes of prior art, the "wherein" clause of claim 27 (lines 3-4) is interpreted as a result of carrying out the claimed method and not a limitation per se.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 16 and 18-24 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,858,701 (of record; "the '701 patent") in view of U.S. Patent No. 5,688,655 (of record; "the '655 patent") as set forth in the previous Office action is maintained for reasons of record and the following***. In addition, new claim 27 is included in this rejection.*** The first factor to consider when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. The '701 patent teaches a drug screening method wherein a preparation of cells that misexpress IRS2 (see, for example, column 4, lines 55-67 to column 5, lines 1-10; column 6, lines 41-57) is used. Note that "misexpression" is defined at column 11, lines 58-60 as including overexpression compared to wild type. The '701 patent further teaches that a given substance or treatment is administered to said test cell or organism which misexpresses IRS2 and then the effect of the substance or treatment on an aspect of IRS2 metabolism is evaluated. For example, an effect on an aspect of IRS2 metabolism is defined as including evaluating a change in IRS2 phosporylation (see column 6, lines 17-33, for example) or in the level of IRS2 binding activity (see column 6, lines 41-57). The '701 patent further teaches a method for evaluating a compound for

the ability to modulate (e.g. to inhibit or promote) the binding of IRS2 polypeptide with an IRS2 binding ligand, e.g., the insulin receptor (see column 6, lines 62-67 through column 7, lines 1-10). Modulation of the formation of the complex in the presence of the compound (e.g., as compared with formation in the absence of the compound) is indicative of a modulation of the interaction between an IRS2 polypeptide and an IRS2 binding ligand (see column 6, lines 62-67 through column 7, lines 1-10).

In summary, the '701 patent teaches a method of determining whether a compound promotes (i.e., activates) or inhibits binding of an IRS2 receptor (i.e., an IRS2-binding protein) to IRS2 by administering the compound to the test cells which "misexpress" (over-express) IRS2 and measuring modulation of an IRS2 mediated signal (e.g., phosphorylation). The limitations of claims 16 and 23 are met because the '701 patent teaches methods wherein a preparation of cells that "misexpresses" IRS2 (see, for example, column 4, lines 55-67 to column 5, lines 1-10; column 6, lines 41-57) is used, wherein "misexpression" is defined at column 11, lines 58-60 as including over-expression compared to wild-type. The '701 patent further teaches that a given substance or treatment is administered to said test cell or organism which misexpresses IRS2 and then the effect of the substance or treatment on an aspect of IRS2 metabolism is evaluated. For example, an effect on an aspect of IRS2 metabolism indicates a change in the level of IRS2 phosphorylation, a change in the level of IRS2 binding activity, a change in IRS2 mRNA levels or a change in IRS2 protein levels in preferred embodiments (see column 6, lines 30-33). The '701 patent also contemplates evaluating the effect of test compounds to inhibit or promote the binding of an IRS

polypeptide and an IRS-2 binding ligand at column 6, lines 62-67 through column 7, lines 1-10. The limitations of claim 18 are met, because the '701 patent teaches a method for evaluating a treatment, wherein the test compound is contacted with cell that includes a reporter gene functionally linked to an IRS2 promoter (see column 7, lines 11-27). Again, throughout the specification of the '701 patent, the misexpression of IRS2 in test cells is discussed, for example, column 4, lines 55-67 to column 5, lines 1-10; column 6, lines 41-57. Note that “misexpression" is defined at column 11, lines 58-60 as including over-expression compared to wild-type. Because overexpression requires genetic engineering techniques, including introducing a vector into the cell in order to overexpress IRS2, the limitation of claim 19 is met. The limitation of claim 20 is suggested, and therefore, rendered obvious by the '701 patent in their discussion of gene therapy (see columns 25-27 and column 28, lines 1-27). Although the '701 patent discusses the use of retroviral viruses for introducing IRS2 in vivo for gene therapy purposes, it would be obvious to one of ordinary skill in the art that such a technique could also be used for introducing IRS2 into a host cell since such techniques are simpler than in vivo gene therapy and were well known in the art, as evidenced by the ‘701 patent. The limitations of claims 21-22 are suggested by the discussion at columns 20 (lines 23-67) and 21 (lines 1-9). The ‘701 patent teaches that 32D myeloid progenitor cells contain no IRS2, thus meeting the limitation of claim 22 (“host cell is a myeloid cell”). The '701 patent teaches expression of IRS2 in FDC-P1 cells in Figure 1, thus meeting the limitation of clam 23. Claim 24 recites “the method of claim 16, wherein the modulation of an IRS2 mediated cellular signal is determined by measuring

the effect on a component of the IRS2 signaling cascade". There is no specific definition of "IRS2 signaling cascade" in the instant specification, however, IRS2 signaling is discussed throughout the background of the invention; a schematic in Fig. 1; and paragraph [0034] of the specification discloses phosphorylation of IRS2 as part of the IRS2 signaling cascade. The '701 patent discusses IRS2 phosporylation as a measure of IRS2 metabolism in their description of their method of evaluating the effects of test compounds (see column 6, lines 17-33, for example):

> In another aspect, the invention features a method of evaluating an effect of a treatment, e.g., a treatment used to treat an insulin-related disorder, or an immune disorder, or a disorder characterized by unwanted cell proliferation. The method uses a test cell or organism which misexpresses an IRS gene (preferably other than IRS-1). In the case where the misexpressed gene is IRS2 the method includes: administering the treatment to a test cell or organism, e.g., a cultured cell, or a mammal, and evaluating the effect of the treatment on an aspect of IRS2 metabolism. An effect on an aspect of IRS2 metabolism indicates an effect of the treatment. In preferred embodiments: the insulin-related disorder is an insulin resistant disease; the effect on an aspect of IRS2 metabolism is a change in the level of IRS2 phosphorylation, a change in the level of IRS2 binding activity, a change in IRS2 mRNA levels, a change in IRS2 protein levels.

Hence, the '701 patent discloses a measure of the IRS2 mediated cellular signaling cascade.

The second factor to consider when making a rejection under 35 U.S.C. 103(a) is to ascertain the differences between the prior art and the claims at issue. The '701 patent does not explicitly teach comparison of the results from a test cell population that over-express IRS2 to a control cell population that produce IRS2 at a lower level (or not at all). The '655 patent teaches a method of determining whether a substance is an inhibitor or an activator of a protein, which comprises: a) providing a test cell which

overproduces a selected protein relative to a control cell which produces said protein at a lower level (or not at all), and wherein production of said protein in said test cell evokes a responsive change in a phenotypic characteristic, b) treating said test cell containing the overproduced selected protein with said substance, and c) examining the treated test cell to determine whether it exhibits a change in said phenotypic characteristic in response to said substance, wherein the examination for a change in phenotypic characteristic in response to said substance includes comparing the response of the treated cell to a comparably treated test cell which does not overproduce the selected protein (see, for example, claims 1-3 of the '655 patent). In summary, the '655 patent teaches a template of drug screening in which a test cell population that over-expresses a protein of interest, or POI, is contacted with a test substance and the results are compared to a control cell population that produces the POI at a lower level (or not at all). The '655 patent explicitly teach this extra step of comparison of effect in a cell population that does not over-express the POI.

The skill in the art of drug screening is high, as evidenced by the ‘655 patent, which is an example of a cell-based assay systems capable of being adapted specifically to various proteins. This segues into the final factor to be considered, which is to consider the objective evidence present in the application indicating obviousness or nonobviousness. There is no evidence of any surprising or unexpected results recited in the claimed methods. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '701 patent by comparing results of the screening tests therein described to a cell population that

produces IRS2 protein at a lower level (or not at all), as taught in '655 patent because the '655 patent teaches that their method:

> "[C]ombines the rapidity and ease of performance of the soft agar assay with a specificity for detecting an active agent exceeding that of the morphology assay. In brief, the method which [described] herein involves the generation of a cell line purposefully engineered to detect both stimulatory and inhibitory agents which are absolutely specific for any given protein which affects the cultural or morphological characteristics of the cell." (See column 2, lines 29-37; emphasis added by the Examiner).

The person of ordinary skill in the art would have been motivated to compare results to a control because the methods of the '655 patent provide "a rapid, yet powerful screening system for the discovery and identification of both inhibitors and activators of proteins...[that] may be applied to virtually any type of protein..." (See column 2, lines 49-53). In summary, the combined teachings of the '701 patent and the '655 patent suggest to one of ordinary skill in the art a method of determining whether a test compound (e.g., a potential therapeutic) is an activator or inhibitor of IRS2 by administering said test compound to a test cell that overexpresses IRS2 and evaluating the effect of said treatment on the metabolism of IRS2 as compared to control. Furthermore, because the methods were well established, the person of ordinary skill in the art could have reasonably expected success. Thus, the claims do not contribute anything non-obvious over the prior art.

Response to Arguments under 35 U.S.C. 103(a)

Applicant argues at p. 6, last paragraph and p. 7, 2nd paragraph: More particularly, and in view of the Examiner's remarks in the Advisory Action regarding what is taught by the '701 patent at col. 6, lines 62 through col. 7, line 10, while the '701 patent teaches a method of determining whether a compound promotes or inhibits

binding of an IRS2-binding protein to IRS2, the method involves detecting the formation of a complex which includes the IRS-2 polypeptide and the IRS-2 binding ligand, and not "examining the test cell for modulation of an IRS2-mediated cellular signal," as recited in claim 16. Thus Applicant asserts that the deficiency in the '701 patent is not just the lack of a comparison to control, but the assay method itself, because the '701 patent only discloses testing the ability of a compound to induce complex formation. The '701 patent does not teach or suggest that that modulation of complex formation between IRS-2 and an IRS2-binding protein by a compound is a measure of the ability of the compound to modulate the activity by binding to the IRS2 complex.

This argument has been fully considered, but is not found persuasive. The '701 patent teaches examining the test cell for modulation of an IRS-2 mediated cellular signal. For example, as pointed out at p. 6 of the Office action mailed 24 February 2009, the '701 patent teaches that assaying for an effect on an aspect of IRS2 metabolism can be carried out by measuring a change in the level of IRS2 phosphorylation, a change in the level of IRS2 binding activity, a change in IRS2 mRNA levels or a change in IRS2 protein levels in preferred embodiments (see column 6, lines 30-33). Further, in the instant specification a schematic of IRS2-mediated cellular signaling is shown in Fig. 1 and paragraph [0034] of the instant specification discloses phosphorylation of IRS2 as part of the IRS2 signaling cascade. Since the '701 patent discusses IRS2 phosporylation as a measure of IRS2 metabolism in their description of their method of evaluating the effects of test compounds (see also column 6, lines 17-33, for example), they are also teaching and suggesting examination of the test cell for modulation of an IRS2-mediated cellular signal. Hence, the '701 patent discloses an IRS2-mediated cellular signal and a measure of the IRS2 mediated cellular signaling cascade.

Applicant argues at p. 7, 1st paragraph that the assay in the '701 patent is silent as to the expression level of IRS2 or any of the cellular components in the assay, with no teaching or suggestion that there would be any reason to compare cells that express different levels of IRS2 or any other cellular component in an assay that simply detects complex formation.

This argument has been fully considered, but is not found persuasive. The '701 patent teaches a drug screening method wherein a preparation of cells that "misexpresses" IRS2 (see, for example, column 4, lines 55-67 to column 5, lines 1-10; column 6, lines 41-57) is used. Note that "misexpression" is defined at column 11, lines 58-60 as including overexpression compared to wild type, thus there is an implicit reference to comparison in the teachings of the '701 patent. The '701 patent further teaches that a given substance or treatment is administered to said test cell or organism which misexpresses IRS2 and then the effect of the substance or treatment on an aspect of IRS2 metabolism is evaluated. Thus the '701 patent is not silent as to the expression level of IRS2. In addition, since the '701 patent teaches measurement of the effect of the test substance or treatment on IRS2 metabolism, the assay is not simply one that detects complex formation. Further, as noted above, the '655 patent teaches a template of drug screening in which a test cell population that over-expresses a POI is contacted with a test substance and the results are compared to a control cell population that produces the POI at a lower level (or not at all), thus the implicit reference to comparison in the '701 patent is explicitly described in the '655 patent. Finally, the instant claims do not recite the "expression level" of IRS2 or any other cellular components, thus Applicant appears to be arguing limitations not present in the claims.

Applicant argues at p. 7, 3rd paragraph that the '655 patent does not remedy the deficiency of the '701 patent (namely, lacking any teaching or suggestion that the ability of a compound to modulate complex formation between IRS2 and an IRS2 ligand is a measure of the ability of the compound to bind to and modulate the activity of the IRS2 complex) because the '655 patent teaches only a relationship between expression of a protein-of-interest (e.g., IRS2) and a phenotype that depends on the activity and level of expression of the protein-of-interest. The '655 patent is silent with regard to any protein that functions in a multi-protein complex.

This argument has been fully considered, but is not found persuasive. First, the '701 patent teaches examining the test cell for modulation of an IRS-2 mediated cellular signal. For example, as pointed out at p. 6 of the Office action mailed 24 February 2009, the '701 patent teaches that assaying for an effect on an aspect of IRS2 metabolism can be carried out by measuring a change in the level of IRS2 phosphorylation, a change in the level of IRS2 binding activity, a change in IRS2 mRNA levels or a change in IRS2 protein levels in preferred embodiments (see column 6, lines 30-33). Further, in the instant specification a schematic of IRS2-mediated cellular signaling is shown in Fig. 1 and paragraph [0034] of the instant specification discloses phosphorylation of IRS2 as part of the IRS2 signaling cascade. Since the '701 patent discusses IRS2 phosporylation as a measure of IRS2 metabolism in their description of their method of evaluating the effects of test compounds (see also column 6, lines 17-33, for example), they are also teaching and suggesting examination of the test cell for modulation of an IRS2-mediated cellular signal. Thus the deficiency of the '701 patent is not that it only measures complex formation. Hence, the '701 patent discloses an IRS2-mediated cellular signal and a measure of the IRS2 mediated cellular signaling cascade.

Applicant asserts at p. 7, 4th paragraph that their methods distinguish between compounds that bind to and modulate IRS2 complex activity in the cell (see, e.g., paragraph [0032]), versus compounds that either bind to an IRS2 complex but do not modulate its activity, or compounds that modulate the IRS2 signal transduction cascade in cells but do so by modifying the biological effects of other intracellular protein or non-protein targets in this pathway. By way of example, insulin would be an activator according to the '701 patent, but not the instant invention.

This argument has been fully considered but is not found persuasive. Applicant appears to be arguing limitations not present in the claims. For instance, there is no requirement in claim 16 or its dependents that the test compound does not modify the biological effects of other cellular proteins. Regarding claim 27, as noted above, this claim is indefinite. In response to Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., their methods distinguish between compounds that bind to and modulate IRS2 complex activity in the cell, citing paragraph [0032]) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, the teachings of the '701 patent disclose the claimed invention and do not merely disclose methods in which compounds either bind to an IRS2 complex but do not modulate its activity or compounds that modulate the IRS2 signal transduction cascade by modifying the biological effects of other intracellular proteins. For example, at column 6, lines 41-55:

> In another aspect, the invention features a method of evaluating an effect of a treatment, e.g., a treatment used to treat an insulin-related disorder, or an immune disorder, or a disorder characterized by unwanted cell proliferation. The method uses a test cell or organism which

> misexpresses an IRS gene (preferably other than IRS-1). In the case where the misexpressed gene is IRS-2 the method includes: administering the treatment to a test cell or organism, e.g., a cultured cell, or a mammal, and evaluating the effect of the treatment on an aspect of IRS-2 metabolism. An effect on an aspect of IRS-2 metabolism indicates an effect of the treatment. In preferred embodiments: the insulin-related disorder is an insulin resistant disease; the effect on an aspect of IRS-2 metabolism is a change in the level of IRS-2 phosphorylation, a change in the level of IRS-2 binding activity, a change in IRS-2 mRNA levels, a change in IRS-2 protein levels.

There is no indication in the passage above that the '701 patent exclusively discloses methods in which compounds either bind to an IRS2 complex but do not modulate its activity or compounds that modulate the IRS2 signal transduction cascade by modifying the biological effects of other intracellular proteins.

Applicant asserts at p. 7, last paragraph that modulation of a target protein's activity by a compound may be direct (i. e., the compound binds to and modulates the activity of a target protein) or indirect (i. e., the compound binds not to the target protein complex but to another cellular component outside the complex to exert its effect). Distinguishing between direct and indirect modulation of a target protein is problematic with targets like IRS proteins, which are "docking" proteins. IRS proteins link the insulin receptor to other intracellular proteins in order to transduce the insulin signal, but have no intrinsic enzymatic activity that can be exploited.

The Examiner takes no issue with Applicant's assertion that modulation may be direct or indirect, however, there is nothing in the instantly claimed methods that distinguishes between direct or indirect modulation. In response to applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., direct or indirect modulation) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues at p. 8, 1st paragraph that the instant method identifies small molecules that are direct modulators, citing the instant specification at paragraph [0032] Applicant further asserts that the sections that the Examiner has cited in the '701 patent suggest that the term "IRS2 binding ligand" of the '701 patent is mistakenly being equated with "compound" of the instant invention, citing the '701 patent at column 6, lines 65-68) that refers to a naturally occurring protein. Applicant further cites a passage from the '701 patent that is asserted to say "nothing about the small molecule of the instant invention that binds to the IRS2 complex."

Applicant's argument has been fully considered but is not found persuasive. The cited passage does not appear to be at column 7, lines 5-10, as Applicant claims, however, the passage cited by Applicant at p. 8 of their Remarks actually discloses test compounds distinctly from the IRS2 binding ligand. There is no mistaking the term "IRS2 binding ligand" for "compound" since the '701 patent teaches a ***compound*** and the evaluation of that ***compound's*** ability to modulate (inhibit or promote) the binding of an IRS2 polypeptide with an IRS2 binding ligand. (See the '701 patent, Col. 6, line 65 through column 7, line 10). There is nothing in this passage that suggests the effect of the compound on the IRS2 binding polypeptide and ligand is not direct. Further, as noted above, there is nothing in instantly claimed methods that distinguishes between direct or indirect modulation. In fact, claim 16, part b) explicitly states that the small molecule can come into contact with IRS2 or a complex comprising IRS2 ***and other cellular proteins in the cell***, so contact with other cellular proteins is not ruled out.

Applicant argues at p. 9, 1st paragraph that the '701 patent remains silent (as it must) with respect to whether or not the compound that causes modulation of the interaction between the IRS2 polypeptide and the IRS2 binding ligand does so by binding to IRS2, the IRS2 binding ligand, another protein or non-protein species present in the assay mixture, or simply modifies the solvent system or chelates or otherwise interferes with necessary ionic components of the assay milieu such that the interaction between IRS2 and the IRS2 binding ligand is altered in some manner. Applicant asserts that the limits of prior methods were understood when conceiving and reducing to practice the invention of the instant application.

Applicant's argument has been fully considered but is not found persuasive. The instant claim 16 and its dependent remains silent with respect as to whether or not the compound that causes modulation of the interaction between the IRS2 polypeptide and the IRS2 binding ligand does so by binding to IRS2, the IRS2 binding ligand, another protein or non-protein species present in the assay mixture, or simply modifies the solvent system or chelates or otherwise interferes with necessary ionic components of the assay milieu such that the interaction between IRS2 and the IRS2 binding ligand is altered in some manner. In fact, claim 16, part b) explicitly states that the small molecule can come into contact with IRS2 or a complex comprising IRS2 ***and other cellular proteins in the cell***, so contact with other cellular proteins is not ruled out. Applicant appears to be arguing limitations not present in the claims. There is no requirement of direct modulation of IRS2 in the instant claims. It is noted that the features upon which Applicant relies (i.e., compound that causes modulation of the interaction between the IRS2 polypeptide and the IRS2 binding ligand does not do so by binding to IRS2, the IRS2 binding ligand, another protein or non-protein species present in the assay mixture, direct or indirect modulation) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, new claim 27 is indefinite (see Rejection under 35 U.S.C., second paragraph, above).

Applicant argues at p. 9, 2nd paragraph that it is pointed out that the '655 patent focuses on target proteins evoking phenotypic responsive changes in cells when

overproduced. The presence of the target protein in a cell causes an observable phenotype whose intensity is related to the level of the activity of the target protein in the cell (i. e., the level of the protein and its specific activity in the presence of a modulator). In this regard, the Examiner has suggested, based on the '701 patent, that IRS2 overexpression results in increased proliferation when IL-4 is added and that this could be the basis for a screening method that identifies compounds that modulate IRS2 function. (Office Action at p. 14). To the contrary, such a method would not distinguish modulators that act on IRS2 (or a complex containing IRS2) from modulators that act on other cellular components. Further, one of ordinary skill in the art would recognize that the screening method disclosed in the '655 patent makes use of the intrinsic enzymatic activity of a cellular enzyme to evoke a phenotype that responds both to the level of the protein and the activity of a protein as modulated by activators or inhibitors that act on that protein to identify modulators of that protein. IRS2 does not have such an activity nor does it evoke such a phenotype.

This argument has been fully considered but is not found persuasive. First, to clarify, the Examiner did not suggest that IRS2 overexpression resulting in increased proliferation when IL-4 is added could be the basis for a screening method that identifies compounds that modulate IRS2 function (citing the Office Action mailed 12 November 2009 at p. 14). At p. 14 of the Office action mailed 12 November 2009, the Examiner was responding to an unrelated argument. The Examiner's point that IRS2 overexpression resulted in increased proliferation when IL-4 was added was to underscore the biological importance of IRS2 on cell growth and insulin signaling pathways. Second, the '655 patent taught comparison between a cell that over-expresses a protein of interest and a control cell which produces said protein at a lower level (or not at all) in their claims, and so was relied upon to show that one of ordinary skill in the art would understand that in a screening assay the explicit comparison between test and control is useful. Applicant's is arguing against the references individually, and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642

F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231

USPQ 375 (Fed. Cir. 1986).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Christina Borgeest

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Examiner, Art Unit 1649